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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/697,703 | 10/31/2003 | H. William Bosch | 029318-0973 | 8369 |

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Elan Drug Delivery, Inc. c/o Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, DC 20007-5109

| EXAMINER | |
|---|---|
| CLARK, SARA E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/697,703 | BOSCH ET AL. | |
| | Examiner | Art Unit | |
| | SARA E. CLARK | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-95* is/are pending in the application.

4a) Of the above claim(s) *32-35,39,41-43 and 45-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,36-38,40 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/2008, 3/9/2009 and 3/27/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***DETAILED ACTION***

Receipt is acknowledged of Applicants' Remarks, filed 3/9/2009.

No claims have been amended and no new claims have been added.

Claims 1-95 are pending: claims 32-35, 39, 41-43, and 45-95 stand withdrawn, while claims 1-31, 36-38, 40, and 44 remain under examination.

***INFORMATION DISCLOSURE STATEMENT***

The information disclosure statement (IDS) submitted on 12/3/2008 was filed prior to the mailing date of the first non-final Office Action on 12/9/2008, and the information disclosure statements (IDS) submitted on 3/9/2009 and 3/27/2009 were filed after the mailing date of the first non-final Office Action on 12/9/2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

***MAINTAINED REJECTIONS***

The following rejections are maintained from the previous Office Action dated 12/9/2008, on the ground that the references cited therein continue to read on the limitations of the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**Rejections under 35 USC §103**

A. Claims 1-15 and 27-31 **stand** rejected under 35 U.S.C. 103(a) as being unpatentable over REINER et al (US Pat. 5,711,961, issued 1/27/1998) in view of RYDE et al. (US 6,375,986, issued 4/23/2002).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

B. Claims 1, 10-13, and 15-26 **stand** rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of LIVERSIDGE et al. (US 5,552,160 see PTO-1449 filed 4/01/2004).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

C. Claims 1 and 16-26 **stand** rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of SINGH et al. (Analytical Profiles of Drug Substances and Excipients, Volume 28, 2001, p197-249) and in view of BOSCH et al. (US 5,510,118).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

D. Claims 1, 36-38, and 40 **stand** rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of SINGH et al. (Analytical Profiles of

Drug Substances and Excipients, Volume 28, 2001, p197-249) and in view of MERCK (The Merck Index 12th ed. Merck & Co. 1996, codeine, p416-417).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

E. Claims 1 and 44 **stand** rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of BUHL et al. (US 5,776,563 see PTO-892 filed 9/5/2007).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

***RESPONSE TO ARGUMENTS***

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the above rejections (A) through (E) under 35 U.S.C. 103(a) have been maintained for the following reasons, in particular clarifying the teachings of Reiner et al., and addressing the rationale to modify Reiner et al. in view of Ryde et al.

Specifically, Reiner et al. disclose the following (col. 1, lines 23-30 and 42-45):

> For drugs which are bitter or have little taste but nevertheless have very rapid release kinetics, tests have therefore also been carried out on coating them with the use of the microencapsulation technique; according to the particular kinetic results to be achieved, sometimes, the microencapsulation technique was not used on the whole of the active ingredient under investigation but only on some of it in order to keep a proportion for immediate action and the rest for delayed action.
>
> Chewing gum preparations are particularly acceptable to children who can ingest drugs with a pleasant taste with the use of a more congenial form of ingestion closer to a normal sweet.

Col. 4, lines 48-67:

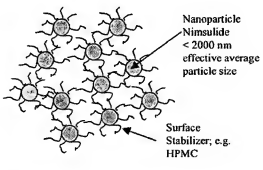
> In the case of unpalatable active ingredients such as . . . **Nimesulide** (50 mg), etc., sugary microgranules are prepared and the various active ingredients subsequently to be mixed with the chewing gum are adsorbed thereon.
>
> These [sugary] microgranules are then coated with the usual excipients and are then mixed with the gums. The technology used and some examples of the application thereof are given by way of non-limiting information:
>
> A. Sugary microgranules of 850 microns diameter were introduced into a vessel provided with automatic spraying equipment and a system for blowing in hot air at 40.degree./80.degree. C. and for recovering the blown air. If the formula requires it, the granules may be moistened with suitable flavouring essences before enlargement with syrup.
>
> B. A syrup, possibly suitably flavoured, **containing the micronized drug** in suspension, was prepared (the mean quantities of drug which can be dispersed vary between 1 and 15% by weight of the syrup).

Thus, Reiner et al. teach that the bitter-tasting drug nimesulide is in micronized form (col. 4, line 65), a term defined in the Remarks (p. 24) to connote particles "in the micron size range," which encompasses drug particle sizes less than 2000 nm (2 microns). The process of Reiner et al. teaches that the micronized nimesulide particles are mixed with a flavored syrup and sprayed onto the surface of comparatively very large (850 micron)

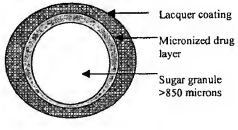
sugary granules. The purpose of the flavored syrup and the sugary granules is to mask the taste of the bitter-tasting micronized nimesulide.

Example 11 of Reiner et al. discloses a 1.55 gram chewing gum tablet containing 50 mg of nimesulide, plus several sweeteners and flavoring agents: 180 mg of sugary microspheres; 458 mg of sorbitol, a sweetener commonly used in chewing gum; 260 mg or sucrose, a natural sweetening agent; 5.2 mg of aspartame, an artificial sweetening agent; and 55.6 mg of orange flavoring. The purpose of all of these components is to mask the bitter taste of the micron-sized particles of nimesulide suspended in a flavored syrup and sprayed onto the surface of the large sugary granules. Thus, not only do Reiner et al. not teach away from the claimed nimesulide nanoparticles, the very object of Reiner et al. is an oral dosage form containing nimesulide particles in the micron size range to promote its dispersal and absorption, plus sweeteners and flavoring agents to mask the bitter taste. This combination has the advantage of improving patient compliance, while at the same time improving the absorption rate of the drug.

Applicants' Remarks supply a useful diagram of the claimed invention contrasted with that of Reiner:




(A) claimed composition




(B) Reiner's chewing gum

Thus, the claimed composition as depicted in (A) is simply a "zoomed-in" view of the micronized drug layer of (B) as disclosed by Reiner et al, minus the surface stabilizer adsorbed onto the surface of the micronized drug particles. The sugary granule particle size is about 850 microns, but the nimesulide particle size sprayed onto the surface thereof is, by Applicant's own admission, in the micron size range, which reads on particle sizes "of less than 2000 nm" (2 microns) of the claimed invention. Therefore, in contrast to point (i) of the Remarks (p. 24), Reiner et al. explicitly teach nimesulide particles in the micron size range, not only teaching nimesulide particles having an effective average particle size less than 1.1 microns (1100 nm) but directly reading on the size limitations recited by instant claims 1-31, 36-38, 40 and 44.

Reiner et al. teach an outer (lacquer) coating having a hydroxypropylmethyl cellulose (HPMC) and polyethylene glycol base (col. 2, lines 46-50; Example 11), which are known in the art as stabilizing, binding, and dispersing agents. However, as pertains to point (ii) of the Remarks (pp. 24-25), Reiner et al. do not disclose such stabilizing agents adsorbed onto the surface of the micron-sized nimesulide particles, specifically, the elected cationic polymeric surface stabilizer polyvinyl-pyrrolidone/vinyl acetate, (PVP/VA) as recited by claim 11. As noted above, this is the only aspect of the claimed invention not disclosed by Reiner et al.

As discussed in the maintained rejection (A), RYDE teaches compositions of solid dose nanoparticles having a poorly soluble active agent, at least one polymeric surface stabilizer, and dioctyl sodium sulfosuccinate (DOSS) whereby upon administration to a human the composition exhibits dramatic redispersion of the

nanoparticles (col. 5, lines 16-23, 55-67), exemplified by the NSAID ketoprofen (tables 1-3), which is structurally similar to nimesulide.

Applicant's central assertion is that one skilled in the art would not have had any reason to improve the redispersibility of nimesulide contained within a chewing gum dosage form, because drug nanoparticles having superior redispersibility would leach from the gum into the patient's mouth, exposing them to the bitter taste of the drug, which is exactly what Reiner et al. try to avoid (p. 25).

However, this is not persuasive because the chewing gum dosage form of Reiner et al. already contains nimesulide nanoparticles in the micron size range, as in the claimed invention. The micronized drug particles are intended to leach into the patient's mouth, because this is how the drug is administered and absorbed, and the consequent bitter taste is the purpose of the flavorings and sweeteners. There would have been no reason to expect that the bitter taste of micronized nimesulide particles would no longer be masked by the flavorings and sweeteners by adsorbing a surface stabilizer onto the surface of the micron-sized nimesulide particles. Rather, there would have been a reason to expect that such a modification could be made to decrease the tendency of the drug to agglomerate, with minimal effect on the taste experienced by the patient.

Therefore, one of ordinary skill in the art would have been motivated to modify the micronized nimesulide chewing gum composition as taught by Reiner et al., with the adsorbed polymeric surface stabilizer Plasdone S630 and nanoparticle sizes under one micron as disclosed by Ryde et al., because both Reiner and Ryde suggest the combination. Reiner et al. address the problem of gastric damage caused by NSAIDs by

using a chewing gum dosage form so that most of the drug is absorbed in the mouth; as well as the problem of the bitter taste of nimesulide particles in the micron size range, by including sweetening and flavoring agents. Ryde et al. address the agglomeration and bioavailability problem by employing drug nanoparticles as small as 200 nm, and surface stabilizers such as Plasdone S630 and DOSS adsorbed onto the surface of the drug nanoparticles. Because there would have been no reason to expect that the advantages of Ryde (enhanced redispersibility and bioavailability) would diminish the advantages of Reiner (palatable taste leading to better patient compliance and less gastric damage), it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the advantages of each, with a reasonable expectation of success.

Applicant further traverses rejections (B), (C), (D), and (E) under 35 U.S.C. 103(a) on the grounds that there is an insufficient motivation to modify Reiner et al. in view of Ryde et al. Because the rationale articulated here overcomes these deficiencies, and no other arguments are presented, rejections (A), (B), (C), (D), and (E) under 35 U.S.C. 103(a) are maintained. It is noted that *novelty* is not the same as and is not sufficient to establish an inventive step, i.e., nonobviousness.

## ***CONCLUSION***

No claims are allowed.

THIS ACTION IS MADE FINAL.

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***CORRESPONDENCE***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612